Interferon

The Magic Bullet to Prevent Hepatocellular Carcinoma Recurrence After Resection?

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Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer in men and the sixth most common cause in women.[1] Its incidence is rising faster than most other cancers due to the increasing prevalence of hepatitis B (HBV) and C (HCV) infection. Among the curative treatments, liver transplantation can only be offered to a small proportion of patients due to graft availability, selection criteria, and high cost. Therefore, liver resection, or perhaps ablation, remains the sole available therapy in many situations. While liver resection can be performed with a mortality rate below 5% in cirrhotic patients with well preserved liver function and an absence of portal hypertension in specialized centers,[2] more than half of these patients developed recurrent HCC within 5 years of surgery despite clear resection margins (R0). Recurrences should be differentiated into 2 categories: early and late recurrences.[3] Early recurrent HCCs are the results of residual hepatic tumors left behind after a presumably R0 resection; usually, such tumors will become apparent within 2 years of surgery. In contrast, late (also called de novo) tumors are new, typically occurring more than 2 years after surgery, as the result of the underlying procarcinogenic liver disease or virus with the highest risk in patients with hepatitis B or C. This distinction is important as neoadjuvant or adjuvant therapies may be effective in only 1 type of recurrence. Another feature that may impact the outcome as well as tolerance of therapies added to liver resection is the presence and severity of the underlying liver disease; for example, in hepatitis B patients, HCC may occur without cirrhosis, while cirrhosis is consistently present in HCC related to HCV.

What are the strategies to improve outcome in patients with resectable HCC?[4,5] One approach is liver transplantation, which theoretically eliminates both the cancer as well as the underlying liver disease. Because of the limited pool of cadaveric donors and the significant risk for a healthy donor in living donation, liver transplantation can be offered only when the tumor characteristics enable good long-term results (eg, Milan criteria: solitary nodule <5 cm or fewer than 3 nodules <3 cm).[6–8] Thus, liver resection, or perhaps tumor ablation, is the only available chance for a cure in most patients with resectable HCC, and logically a timely focus is the search for effective neoadjuvant or adjuvant strategies to prevent both early and de novo recurrences after surgery. Surprisingly, only few convincing data are available.[4,9]

Systemic and local chemotherapies, oral administration of acyclic retinoids, transarterial chemoembolization (TACE), irradiation with lipiodol-iodine 131, and immunotherapy have been tested as neoadjuvant or adjuvant options after hepatic resection for HCC. Although a review found no convincing benefit of either systemic or local adjuvant chemotherapy,[4] a recent case-control study reported improved overall and disease-free survival for stage I/II disease (eg, tumors <5 cm)[10] after adjuvant intraportal chemotherapy.[11] Another promising adjuvant therapy after resection for HCC is the oral administration of acyclic retinoids, which was associated with a significant lower incidence of

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ISSN: 0003-4932/07/24506-0843
DOI: 10.1097/SLA.0b013e31805d0788

recurrence in a randomized control trial (RCT) compared with the placebo group (27% vs. 45%).[12] The anticancer effects of retinoids may be conferred through the deletion of malignant clones before the minimal residual disease becomes clinically detectable after liver resection.[13] Additionally, adjuvant intrahepatic irradiation with transarterial applied lipiodol-iodine 131 significantly lowered recurrence rates and improved patient survival after liver resection for HCC.[14,15] In contrast, neoadjuvant TACE before resection failed to be effective in 2 RCTs.[16,17]

Adoptive immunotherapy and immunotherapy with interferon (IFN) have been examined in the adjuvant setting after liver resection or ablation for HCC.[4] To date, 6 RCTs from Asia[18–24] and one from Europe[25] reported on the adjuvant effects of IFN after liver resection[18–20,23–25] or tumor ablation[21,22] for HCC (Table 1).

One of these trials is reported in this issue of the *Annals of Surgery*.[24] These authors designed a large open-label RCT in 86 cirrhotic patients who underwent a curative (R0) resection mostly (>95%) related to HBV. This well-established group in the field of liver surgery and transplantation tested the effects of interferon α-2b (IFN-α) given postoperatively 3 times a week for 6 weeks. IFN-α is an appealing cytokine because it yields a variety of biologic properties, including antiviral, immunomodulatory, antiproliferative, and antiangiogenic effects. A particular feature of this study was the use of 2 high doses of IFN-α (10 MIU/m^2 and 30 MIU/m^2). Indeed, the high-dose arm of 30 MIU/m^2 was terminated prematurely due to the high incidence of severe side effects such as grade 3 hematologic toxicity. In the 10 MIU/m^2 group, adherence to the treatment was surprisingly high when compared, for example, with the recently published RCT by Mazafferro et al, where adherence in HCV patients was only 37%, despite the fact that the IFN-α dose was considerably lower (3 MIU).[25] Another RCT, including patients receiving 3 MIU 3 times a week, was discontinued due to the high incidence of adverse events/dropout.[26] There might be a different perception of adverse events in the Asian population since the given dose is remarkably higher in the Asian trials (Table 1).

While the present study failed to show a significant effect in terms of tumor recurrence or patient survival for the entire study population, IFN-α was found to prevent early recurrent disease in the subgroup of patients with advanced disease (stage III/IVA), which includes multiple tumors larger than 5 cm or a tumor involving a major branch of the portal or hepatic vein(s).[10] This regimen also impressively improved the 5 years survival of this subpopulation (24% control arm vs. 68% treatment arm). Furthermore, IFN-α prevented early but not late recurrence, a finding that is consistent with 2 other RCTs from Asia in HBV patients,[18,23] but in sharp contrast to the recent Italian RCT by Mazzaferro et al in hepatitis C patients[25] (Table 1). In hepatitis C patients, protective effects of IFN have been documented only on late recurrences.[19,20,25] Lo et al speculate on possible mechanisms to explain their observation that IFN-α acts on the early progression of residual micrometastasis after liver resection, while others could see an effect only on late, possibly, de novo tumors.[24] These authors think that IFN-α likewise acts through its antitumor and antiangiogenic properties, although such an effect was not observed in patients with advanced HCC who were not suitable for surgical therapy.[26]

A potential reason for the discrepant findings between the Western and current Asian RCT may be attributed to the different composition of the study populations. While the Hong Kong trial included a vast majority of patients with

TABLE 1. RCT Investigating Adjuvant Effects of IFN After Resection or Ablation of HCC

Reference (year)	Intervention	IFN	IFN (n)	Control (n)	IFN Dose	HCV (n)	HBV (n)	HCV+ HBV (n)	Outcome
Ikeda et al[18] (2000)	Resection, n = 16; ethanol, n = 4	IFN-α	10	10	6 MIU 2× weekly for 36 mo	20	0	0	Early recurrence ↓
Kubo et al[19,20] (2001, 2002)	Resection	IFN-α	15	15	6 MIU daily for 2 wk, 3× weekly for 14 wk, and 2× for 88 wk	30	0	0	Late recurrence ↓ and improved long-term survival
Shiratori et al[21]	Ethanol	IFN-α	49	25	6 MIU 3× weekly for 48 mo	74	0	0	No impact on 1st recurrence but reduced 2nd and 3rd recurrence
Lin et al[22] (2004)	Ethanol	IFN-α	20	10	3 MIU 3× weekly every mo; 3 MIU daily for 10 d every mo	13	16	1	Late recurrence ↓ and improved 4-yr survival
Sun et al[23] (2006)	Resection	IFN-α	118	118	3 MIU 2× weekly for 2 wk followed by 5 MIU 3× weekly	0	236	0	Early recurrence ↓ and improved long-term survival
Mazaffero et al[25] (2006)	Resection	IFN-α	76	74	3 MIU 3× weekly for 48 wk	80	0	70	No effect on overall recurrence but late recurrence ↓ for pure HCV
Lo et al[24] (2007)	Resection	IFN-α	40	40	10 MIU/m^2 3× weekly for 16 wk	2	77	1	Early recurrence ↓ and improved 5-yr survival for stage III/IVA

MIU indicates million IU.

HBV infections and only 3 patients (3%) with HCV,[24] all patients of the Italian trial were HCV infected, with 46% of the patients being co-infected with HBV.[25] The results of the Hong Kong trial are, however, consistent with a recently published large RCT,[23] which also included only patients with pure HBV. The RCT by Lo et al[24] also had a higher proportion of patients with advanced disease (stage III/IV) compared with the trial by Mazzaferro et al[25] (51% vs. 39%). The patients are therefore at a higher risk of early recurrences due to minimal residual tumor. Why interferon treatment was found effective only in large HCC remains unclear. Possibly, the relatively small number of patients with an early stage of the disease associated with the low incidence of recurrence might have precluded detecting a difference (type II error).

Whether IFN-α also has indirect effects on late recurrent HCC through protective effects on the underlying viral disease cannot be answered by the current RCT. To better understand the effects of IFN-α, it would have been valuable to have more information about viral parameters under adjuvant therapy.

In conclusion, all 7 RCTs showed beneficial effects of adjuvant IFN treatment, either for the entire study population or defined subpopulations, after hepatic resection or ablation for HCC. The effect seems particularly striking for patients with pure HBV infections. These data are highly encouraging and should lead the search for new strategies, for example, by using a more stable formula and constant delivery of IFN through pegylated IFN, or through the use of nucleoside (eg, lamivudine) or nucleotide (eg, adefovir dipivoxil) analogues alone in HBV patients and the combination of IFN with ribavarin in HCV patients. Importantly, any new strategy must still be tested in RCTs, including a control group without treatment. It is likely that liver resection may gain wider acceptance with the venue of highly effective adjuvant therapy.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: Globocan 2000. *Int J Cancer*. 2001;94:153–156.
2. Clavien PA, Petrowsky H, De Oliveira ML, et al. Strategies for safer liver surgery and transplantation of partial liver grafts. *N Engl J Med*. 2007;356:1545–1559.
3. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*. 2003;362:1907–1917.
4. Colombo M, Donato MF. Prevention of hepatocellular carcinoma. *Semin Liver Dis*. 2005;25:155–161.
5. McCormack L, Petrowsky H, Clavien PA. Surgical therapy of hepatocellular carcinoma. *Eur J Gastroenterol Hepatol*. 2005;17:497–503.
6. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334:693–699.
7. Hiatt JR, Carmody IC, Busuttil RW. Should we expand the criteria for hepatocellular carcinoma with living-donor liver transplantation? —No, never. *J Hepatol*. 2005;43:573–577.
8. Clavien PA. Third forum on liver transplantation: living donor liver transplantation. Who needs it? How to do it? Who should do it. *J Hepatol*. 2005;43:11–12.
9. Schwartz JD, Schwartz M, Mandeli J, et al. Neoadjuvant and adjuvant therapy for resectable hepatocellular carcinoma: review of the randomised clinical trials. *Lancet Oncol*. 2002;3:593–603.
10. Wildi S, Pestalozzi BC, McCormack L, et al. Critical evaluation of the different staging systems for hepatocellular carcinoma. *Br J Surg*. 2004;91:400–408.
11. Chau GY, Lui WY, Tsay SH, et al. Postresectional adjuvant intraportal chemotherapy in patients with hepatocellular carcinoma: a case-control study. *Ann Surg Oncol*. 2006;13:1329–1337.
12. Muto Y, Moriwaki H, Ninomiya M, et al. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma: Hepatoma Prevention Study Group. *N Engl J Med*. 1996;334:1561–1567.
13. Takai K, Okuno M, Yasuda I, et al. Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma: updated analysis of the long-term follow-up data. *Intervirology*. 2005;48:39–45.
14. Lau WY, Leung TW, Ho SK, et al. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet*. 1999;353:797–801.
15. Boucher E, Corbinais S, Rolland Y, et al. Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of hepatocellular carcinoma. *Hepatology*. 2003;38:1237–1241.
16. Wu CC, Ho YZ, Ho WL, et al. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. *Br J Surg*. 1995;82:122–126.
17. Yamasaki S, Hasegawa H, Kinoshita H, et al. A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. *Jpn J Cancer Res*. 1996;87:206–211.
18. Ikeda K, Arase Y, Saitoh S, et al. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor: a prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology*. 2000;32:228–232.
19. Kubo S, Nishiguchi S, Hirohashi K, et al. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma: a randomized, controlled trial. *Ann Intern Med*. 2001;134:963–967.
20. Kubo S, Nishiguchi S, Hirohashi K, et al. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. *Br J Surg*. 2002;89:418–422.
21. Shiratori Y, Shiina S, Teratani T, et al. Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med*. 2003;138:299–306.
22. Lin SM, Lin CJ, Hsu CW, et al. Prospective randomized controlled study of interferon-alpha in preventing hepatocellular carcinoma recurrence after medical ablation therapy for primary tumors. *Cancer*. 2004;100:376–382.
23. Sun HC, Tang ZY, Wang L, et al. Postoperative interferon alpha treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. *J Cancer Res Clin Oncol*. 2006;132:458–465.
24. Lo CM, Liu CL, Chan SC, et al. A randomized controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. *Ann Surg*. 2007;245:831–842.
25. Mazzaferro V, Romito R, Schiavo M, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology*. 2006;44:1543–1554.
26. Llovet JM, Sala M, Castells L, et al. Randomized controlled trial of interferon treatment for advanced hepatocellular carcinoma. *Hepatology*. 2000;31:54–58.